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***In: 17th International Symposium on Pediatric Neuro-Oncology (ISPNO).
12-15 June 2016, Liverpool, UK: Oxford University Press.***

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This is the authors' manuscript of an abstract for a paper that was presented at the 17th International Symposium on Pediatric Neuro-Oncology (ISPNO) and published in *Neuro-Oncology* by Oxford University Press.

DOI link to final published version:

<http://dx.doi.org/10.1093/neuonc/now076.75>

Date deposited:

24/08/2016

Embargo release date:

01 June 2017



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Centralised molecular pathology for rare tumours: A national feasibility study of real-time medulloblastoma diagnostics

Advanced diagnostic molecular pathology is becoming essential in contemporary clinical care; however, coordinated multi-centre approaches in rare diseases present specific challenges of centralisation, tissue/assay quality control, standardisation and rapid reporting. We undertook a national study in medulloblastoma (MB), to establish feasibility of rapid sample collection, consent, transportation, centralised pathology review (CPR) and assessment of established prognostic biomarkers, to underpin routine diagnostics and participation in international studies.

Frozen and FFPE tissues were co-submitted to a National Reference Centre, which aimed to report results within 30 days post-surgery. 135 samples were received from 16 centres (2009-present); complete CPR and biomarker analysis was achieved in 87% (118/135), with insufficient material the most common cause of failure. Late reporting was most often due to delayed submission. Twenty (15%) showed high-risk *MYC/MYCN* amplification; iFISH methods best reflected amplification status (vs. MLPA and 450K-derived copy number). β -catenin IHC showed significant inter-observer variability; use of non-IHC methods (*CTNNB1* mutation, chromosome 6 status, 450K subgrouping) allowed more faithful definition of favourable-risk MB_{WNT} status (14/135; 10%). CPR assigned variant (n=30) or modified the local diagnosis (n=10) in 40/135 (30%). Tumour material was assessed for use in contemporary genome-wide methods and was typically suitable for DNA methylation profiling (450K; 129/135, 94%), but commonly fell below QC requirements for RNA-seq (53/135, 39%).

Delayed sample receipt, or submission of inadequate biopsies, represent significant risks to successful centralised diagnostics and investigative biological studies of rare tumours. Validation and stringent QC of specific biomarker assays is essential for robust treatment-stratification in molecularly-driven clinical trials.